BIOLOGIC ORGANIZATION AND THE CANCER PROBLEM*

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The study of growth and development in living organisms has yielded innumerable descriptions of the details of structure at many stages. Fragmentary information is available concerning the physical and chemical requirements for the initiation of cell division. Cytologists and histologists have provided many static pictures of stages in the process of proliferation. The brilliant work of Warren Lewis has added a necessary dynamic element to these studies. Following multiplication, the conversion of blastema cells into specialized cells having characteristic form and internal configuration has made possible a classification of cell types that is clear and for the most part unmistakable. But virtually nothing is known of dynamic processes whose end-result is histologic differentiation. Best known of all is the integration of cell types in organ formation and the development of the organism as a whole. Here, again, descriptions of the stages are plentiful, but knowledge of the mechanisms, whose end-result the stages are, is practically non-existent. In a recent penetrating study, Sinnott has shown that organ form in the cucurbits is unrelated to cell number, size, or type and is, therefore, in all probability, independent of cell proliferation and cell differentiation.

Time slices of the space-time continuum of the growing organism are known, but the dynamic control, regulation, and integration of the whole is still the "Philosopher's Stone" of the biologist. Growth and development still have as a central problem the determination of the factor, or factors, which controls the pattern or configuration of the living whole.

"The Greeks had a name for it." Aristotle called the controlling agent "Entelechy." In the modern period Driesch revived the term and imputed to it super-biologic properties. Spemann's

* Aided by grants from the Josiah Macy, Jr. Foundation and the Jane Coffin Childs Memorial Fund for Medical Research. Read at the Third International Cancer Congress, Atlantic City, September, 1939.

"Embryonic Field" and Weiss' "Biologic Field," while brilliantly conceived symbols for the process, hide ignorance behind a term which cannot be subjected to direct definition or measurement. Child made a great step forward when he demonstrated the importance of "physiological gradients" in determining organization. These gradients can be measured quantitatively and defined with considerable accuracy, and hence come nearer to the answer to the problem than do qualitative descriptions.

It is clear to all biologists that here exist two probably related problems, which may perhaps be partially separable. The first is the determination of the factors which initiate cell division. The second is a rigorous and accurate definition of the control of cellular and organismic configuration.

Students of the cancer problem have been largely, if not entirely, concerned with a search for agents which initiate proliferation. Multiplication of cells is only one of the characteristics of atypical growth. Such differentiation, such evidence of organization as is present, is limited and difficult of accurate determination. Hence the present search for carcinogenic agents.

But it is possible that this is a misplaced emphasis. The initiation of cell proliferation is a constant concomitant of all living things, present in health as well as in disease, in normal processes as well as in the process of repair. It may be taken for granted that there are inherent in all living things factors which, under normal conditions, initiate cell multiplication. Important as it is to determine the physical and chemical conditions necessary to start growth, it is equally vital to know what controls growth subsequently, for it is very obvious that profound derangement of this control is a necessary concomitant of the unrestrained growth of cancerous tissue.

What has been said here is a truism familiar to many biologists, but because there are few clues to the nature of organismic control, it is customarily kept on the top shelf in a dark corner, too valuable to be discarded, too troublesome to be tolerated in the laboratory.

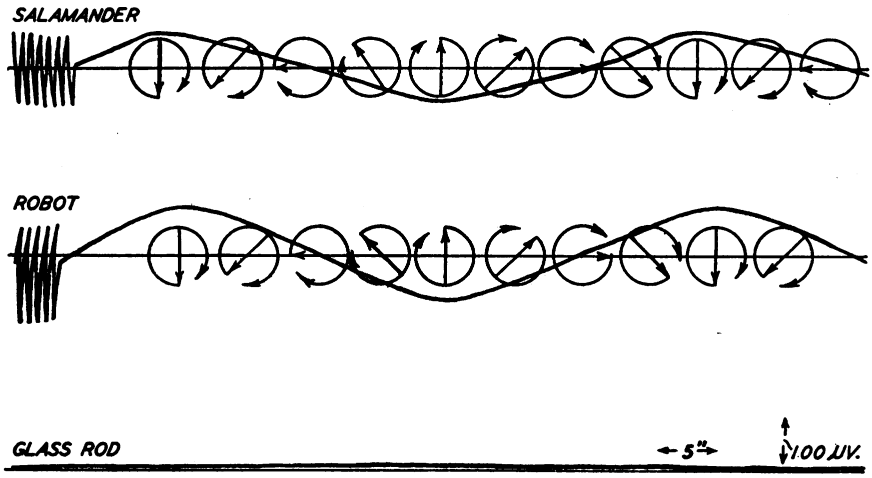
However, the situation is not hopeless. Recent studies have suggested a new approach to organization, an approach which makes possible accurate quantitative definition and measurement. In the hundred and fifty years which have elapsed since Galvani's famous description of the behavior of frogs' legs suspended by a copper wire from an iron railing, the electrical nature of life has been dealt with as a scientific curiosity, or as a basis for quack diagnosis and treatment. Not until the development of the electrocardiograph and, more recently, the electroencephalograph, were electrical phenomena admitted into the legitimate family circle. However, implicit in many of the studies has been the suggestion that all living systems possess relatively stable potential differences. While students have recognized their presence, they have been regarded usually as necessary evils—to be ignored or disregarded in favor of the more exciting wave phenomena of the alternating current output of heart and nervous system. Furthermore, the older technics of electrical measurements were complicated by the difficulty in separating voltage, current, and resistance. The development of the modern radio vacuum-tube and its application to bridge circuits has resolved this difficulty so that now it is possible to determine the voltage differences present in any circuit, relatively independent of changes in current and resistance. This means that it is now possible to study carefully one of the principal properties of electricity without the complication of two other variables, current and resistance. The Burr-Lane-Nims technic, described in 1935, has led to an extensive examination of the electrical properties of living beings. Out of these studies has come a number of interesting conclusions.

In the first place, it is quite evident that wherever there is life there is electricity. This means that electrical phenomena are as much an inherent property of protoplasm as are irritability, metabolism, and reproduction. Moreover, voltage differences are not chaotic, but are organized into characteristic patterns correlated with species, with age, and, in all probability, with the individual. The over-all patterns are relatively stable and seem to be modified only by changes in fundamental biological activity, such as the growth and development of the embryos of Obelia, the salamander, and the chick, the profound disturbances in the generative tract incident on ovulation, and, more interesting in this connection, some phases of the appearance of atypical growths in experimental mice. Burr, Smith, and Strong have recorded the observation that in genetically controlled strains of mice, spontaneous adenocarcinoma of the mammary gland can be recognized by a change in the electrical pattern of potential differences some weeks before it is evident as a result of palpation. Moreover, there is also a significant difference in electrical pattern between the cancer-susceptible mice and cancer-resistant mice. These studies have been extended to an examination of electrical correlates of atypical growth resulting from injection of a carcinogenic agent beneath the skin and from painting of the skin with a similar chemical. The results point clearly to the very real probability that in spontaneous cancer and in chemically produced cancer, a profound change occurs in those controls of growth and differentiation which have electrical correlates.

Here, then, is a new clue to the mechanisms of growth and development. If it be followed, one is brought face to face with a rather startling conclusion. It is an axiom of physics that wherever current flows through a conductor between two points of different potential an electrical field appears. Moreover, the lines of force of such a field determine the orientation and position of all charged particles which come within its sphere. Recently, Teorell has shown that the membrane potential creates a field whose lines of force determine the movement of ions through the membrane, and also the position of all charged ions in the solutions separated by that membrane. If, then, potential differences of characteristic pattern are found in living beings, the passage of the resulting direct current through the conducting medium of protoplasm must set up an electrical field. Since phase boundaries or membranes exist in all cellular mechanisms, it follows that such fields must have importance in determining the arrangement of the units of the pattern of cellular configuration. However, logical inference is one thing, experimental demonstration is another. It is one thing to infer the presence of a field, it is another to demonstrate it in the laboratory. For, even though a field be demonstrated, it is still necessary to ascertain whether the field is a by-product of the living process or a determiner of it. Fortunately, it is possible to demonstrate the field in a living organism by two methods.

While studying the electrical correlates of development in the embryo of the salamander and of the chick, Burr and Hovland observed that the potential gradients between head and tail were not confined to the animal itself but could be detected at a point from 1 to 1.5 mm. distant from the surface. Inasmuch as the embryos live in a conducting medium, it might be expected that such voltages and currents as exist would be short-circuited by the external shunt. Such is evidently not the case. Instead, lines of force in that medium can be intercepted by suitable electrodes, indicating ionic movement determined by field forces. Moreover, a definite approach gradient can be plotted running from maximum, at contact with the embryo, to zero, several millimeters outside. These findings can be explained only by the existence in the living organism of an electrodynamic field.

While pursuing the above studies, a somewhat surprising observation was made. In the early tail-bud stage, embryos of salamanders can be seen to rotate slowly within the jelly capsule, propelled by epidermal cilia. If, under these conditions, microelectrodes are introduced into the capsule and brought to within a fraction of a millimeter of the head and tail of the embryo, slow oscillations of the galvanometer parallel the rotation. The differences are small and difficult to record. However, by substituting a free-



swimming larva for the embryo, and mechanically rotating it on a turntable, the same results are obtained in a form which can be recorded. If a recording galvanometer is used, it is seen that the rotation of the animal gives rise to an alternating sine wave electrical output similar to that of an electrical generator, differing only in the magnitude and frequency. In other words, the animal is behaving like the armature of a dynamo revolved mechanically between brushes. Because the armature has a field, alternating current appears in the circuit of the brushes. Because an alternating voltage of the same character appears in the circuit of the electrodes, and only a field can produce this, it follows that the animal possesses a true field.

To guard against artefacts of technic, an electrical field produced by a piece of copper with a drop of solder at one end was revolved under the same conditions as was the salamander. The recording galvanometer showed exactly the same kind of curve. Similarly, an inert piece of glass tubing, substituted for the living organism, showed no electrical output whatever.

It is impossible to avoid the conclusion that living mechanisms possess electrodynamic fields, and that they are stable, being modified only by profound changes in biologic activity. Growth and development produce just as significant variations in the electrical pattern as do heart and brain waves, the activity of the generative tract associated with ovulation, the development of cancer, and in all probability many as yet undiscovered functions of the living organism.

It is inconceivable that such a widespread phenomenon should be a by-product of life, for it is so intimately bound up with fundamental biological processes that it disappears at death. It may well be, therefore, that here lies the long-sought clue to the problem of organization, disturbance of which results, among other things, in the wild, unrestrained, atypical growth of cancer.